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Ottawa Hull KIA 0C9

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(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

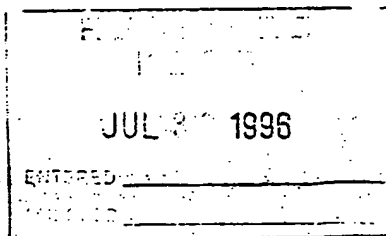
(54) Substituted N-Heteroaroylguanidines, a Process for Their
Preparation, Their Use as a Medicament or Diagnostic
Agent, and a Medicament Containing Them

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(57) 17. Claims.



Notice: This application is as filed and may therefore contain an
incomplete specification.



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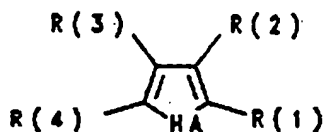
HOE 94/F 094

Dr.v.F.

Abstract

Substituted N-heteroaroylguanidines, a process for their preparation, their use as a medicament or diagnostic agent, and a medicament containing them

The invention relates to heteroaroylguanidines of the Formula I



in which the substituents HA and R(1) to R(5) have the meanings given in claim 1.

These compounds exhibit very good antiarrhythmic properties, as are important for treating diseases which occur, for example, in association with symptoms of oxygen deficiency. As a consequence of their pharmacological properties, the compounds are outstandingly suitable for use as antiarrhythmic pharmaceuticals possessing a cardioprotective component for the prophylaxis and treatment of infarction and for the treatment of angina pectoris, in connection with which they also inhibit or strongly reduce, in a preventive manner, the pathophysiological processes associated with the genesis of ischemically induced damage, in particular associated with the elicitation of ischemically induced cardiac arrhythmias. On account of their protective effects against pathological hypoxic and ischemic situations, the compounds of the formula I according to the invention can, as a consequence of inhibiting the cellular Na⁺/K⁺ exchange mechanism, be used as pharmaceuticals for treating all acute or chronic damage elicited by ischemia, or diseases induced primarily or secondarily thereby. This is the case with regard to their use as pharmaceuticals for surgical interventions,

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for example in organ transplantations, where the compounds can be used both for protecting the organs in the donor prior to and during removal, for protecting organs which have been removed, for example when they are being treated with or stored in physiological bathing fluids, and when transferring the organs into the recipient. The compounds are likewise valuable protective pharmaceuticals to be used when carrying out angioplastic surgical interventions, for example on the heart or on peripheral vessels. In conformity with their ability to protect against ischemically induced damage, the compounds are also suitable for use as pharmaceuticals for the treatment of ischemias of the nervous system, in particular of the CNS, in connection with which they are suitable, for example, for the treatment of stroke or cerebral edema. Over and above this, the compounds of the formula I according to the invention are also suitable for use in the treatment of forms of shock, such as, for example, allergic, cardiogenic, hypovolemic and bacterial shock.

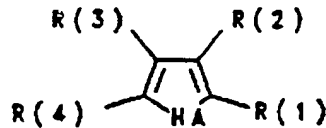
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Hoechst Aktiengesellschaft HOE 94/F 094 Dr. v. F.

Description

Substituted N-heteroarylguanidines, a process for their preparation, their use as a medicament or diagnostic agent, and a medicament containing them

- 5 The invention relates to heteroarylguanidines of the formula I



in which:

HA is SO_m , O, or NR(5),

m is zero, 1 or 2,

10 R(5) is hydrogen, (C_1-C_8) -alkyl or $-C_{am}H_{2am}R(81)$,

am is zero, 1 or 2

R(81) is (C_3-C_8) -cycloalkyl, or phenyl

15 which is not substituted or is substituted by 1-3 substituents from the group F, Cl, CF_3 , methyl, methoxy or NR(82)R(83), with R(82) and R(83) being H or CH_3 ;

or

20 R(81) is (C_1-C_9) -heteroaryl

which is linked via C or N and which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF_3 , CH_3 , methoxy, hydroxyl, amino, methyl-amino, or dimethylamino;

25 one of the two substituents R(1) and R(2)

is $-CO-N=C(NH_2)_2$,

and whichever is the other is

hydrogen, F, Cl, Br, I, (C_1-C_3) -alkyl, $-OR(6)$, C_rF_{2r+1} , $-CO-N=C(NH_2)_2$ or $-NR(6)R(7)$,

30 R(6) and R(7) are, independently, hydrogen or (C_1-C_3) -alkyl,

r is 1, 2, 3 or 4,

R(3) and R(4) are, independently of each other,
hydrogen, F, Cl, Br, I, $-C\equiv N$, $X-(CH_2)_p-(C_q-F_{2q+1})$,
R(8)-SO_{bm}, R(9)R(10)N-CO, R(11)-CO-

5 or R(12)R(13)N-SO₂-,

where the perfluoroalkyl group is straight-chain
or branched,

X is oxygen, S or NR(14),

R(14) is H or (C₁-C₃)-alkyl,

10 bm is zero, 1 or 2,

p is zero, 1 or 2,

q is zero, 1, 2, 3, 4, 5 or 6,

R(8), R(9), R(11) and R(12) are, independently,

15 (C₁-C₈)-alkyl, (C₃-C₆)-alkenyl, $-C_nH_{2n}$ -
R(15) or CF₃,

n is zero, 1, 2, 3 or 4,

R(15) is (C₃-C₇)-cycloalkyl, or phenyl

which is not substituted or is substi-
tuted by 1-3 substituents from the group

20 F, Cl, CF₃, methyl, methoxy or NR(16)R(17)

with R(16) and R(17) being H or C₁-C₄-
alkyl,

where R(9), R(11) and R(12) also have the meaning
of H,

25 R(10) and R(13) are, independently,

H or (C₁-C₄)-alkyl,

where R(9) and R(10) and also R(12) and R(13) can
together be 4 or 5 methylene groups, of which one

30 CH₂ group can be replaced by oxygen, S, NH, N-CH₃
or N-benzyl,

or

R(3) and R(4) are, independently of each other,

(C₁-C₈)-alkyl or $-C_{al}H_{2al}R(18)$,

al is zero, 1 or 2,

35 R(18) is (C₃-C₈)-cycloalkyl, or phenyl

which is not substituted or is substi-
tuted by 1-3 substituents from the group

F, Cl, CF₃, methyl, methoxy or
NR(19)R(20), with R(19) and R(20) being H

or CH₃;

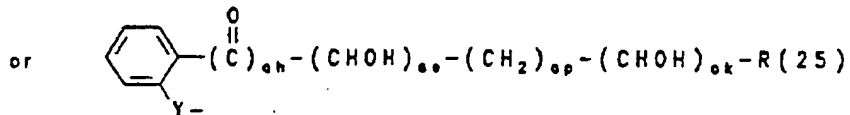
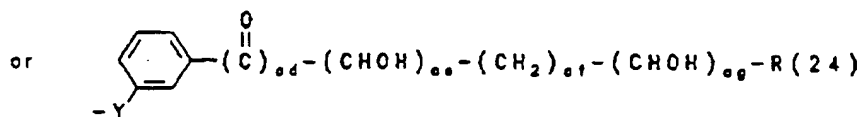
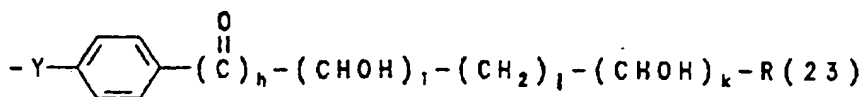
or

R(3) and R(4) are, independently of each other,
(C₁-C₉)-heteroaryl,

5 which is linked via C or N and which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino or dimethylamino;

or

10 R(3) and R(4) are, independently of each other,



Y is oxygen, -S- or -NR(22)-,

h, ad and ah are, independently, zero or 1,

i, j, k, ae, af, ag, ao, ap and ak are, independently, zero, 1, 2, 3 or 4,

15 where, however, in each case,

h, i and k are not simultaneously zero,

ad, ae and ag are not simultaneously zero, and

ah, ao and ak are not simultaneously zero,

R(23), R(24), R(25) and R(22) are, independently,
20 hydrogen or (C₁-C₃)-alkyl,

or

R(3) and R(4) are, independently of each other,
hydrogen, F, Cl, Br, I, CN, (C₁-C₈)-alkyl, (C₁-C₈)-
perfluoroalkyl, (C₃-C₈)-alkenyl or -C₉H₂₉R(26),

25 g is zero, 1, 2, 3 or 4,

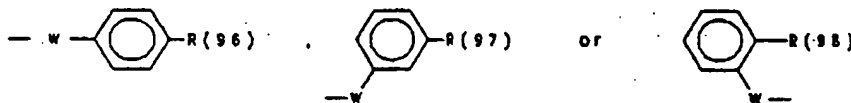
R(26) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl or naphthyl,
 where the aromatic radicals are not substituted or are substituted by 1-3 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(27)R(28), with R(27) and R(28) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

or

R(3) and R(4) are, independently of each other, SR(29), -OR(30), -NR(31)R(32) or -CR(33)R(34)R(35); R(29), R(30), R(31) and R(33) are, independently, -C_aH_{2a}-(C₁-C₉)-heteroaryl which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino or dimethylamino, a is zero, 1 or 2, R(32), R(34) and R(35) are, independently of each other, defined as R(29), or are hydrogen, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

or

R(3) and R(4) are, independently of each other,



R(96), R(97) and R(98) are, independently, (C₁-C₉)-heteroaryl, which is linked via C or N and which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino, dimethylamino or benzyl, W is oxygen, S or NR(36)-, R(36) is H or (C₁-C₄)-alkyl,

or

R(3) and R(4) are, independently of each other,

R(37)-SO_{cm} or R(38)R(39)N-SO₂-,

cm is 1 or 2,

R(37) is (C₁-C₈)-alkyl, (C₁-C₈)-perfluoroalkyl,
(C₃-C₈)-alkenyl or -C_BH_{2B}-R(40),

5 B is zero, 1, 2, 3 or 4,

R(40) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl
or naphthyl,

10 where the aromatic radicals are not substituted or are substituted by 1-3 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(41)R(42), with R(41) and R(42) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

15 R(38) is H, (C₁-C₈)-alkyl, (C₁-C₈)-perfluoroalkyl,

(C₃-C₈)-alkenyl or -C_wH_{2w}-R(43),

w is zero, 1, 2, 3 or 4,

20 R(43) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl or naphthyl where the aromatic radicals are not substituted or are substituted by 1-3 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(44)R(45), with R(44) and R(45) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl,

25 R(39) is H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl,

30 where R(38) and R(39) can together be 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

or

R(3) and R(4) are, independently of each other,

R(46)X(1)-,

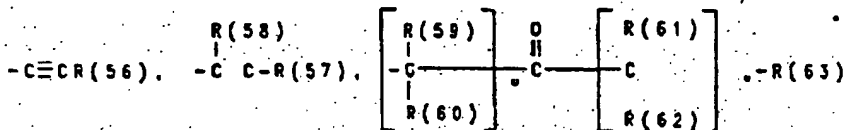
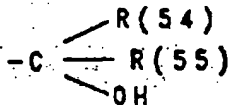
35 X(1) is oxygen, S, NR(47), (D=O)A- or NR(48)C=MN^(*)R(49)-,

M is oxygen or S,

A is oxygen or NR(50),

D is C or SO,

- R(46) is (C_1-C_8) -alkyl, (C_3-C_8) -alkenyl,
 $(CH_2)_b C_d F_{2d+1}$ or $-C_x H_{2x} - R(51)$,
 b is zero or 1,
 d is 1, 2, 3, 4, 5, 6 or 7,
 x is zero, 1, 2, 3 or 4,
 R(51) is (C_3-C_8) -cycloalkyl, phenyl,
 biphenyl, naphthyl,
 where the aromatic radicals are not
 substituted or are substituted by
 1-3 substituents from the group F,
 Cl, CF_3 , methyl, methoxy or
 NR(52)R(53); with R(52) and
 R(53) being H, (C_1-C_4) -alkyl or
 (C_1-C_4) -perfluoroalkyl;
 R(47), R(48) and R(50) are, independently,
 hydrogen, (C_1-C_4) -alkyl or (C_1-C_4) -
 perfluoroalkyl,
 R(49) is defined as R(46), where
 R(46) and R(47) and, respectively, R(46) and R(48)
 can together be 4 or 5 methylene groups, of which
 one CH_2 group can be replaced by oxygen, S, NH,
 N- CH_3 or N-benzyl,
 where A and N(*) are bonded to the phenyl nucleus
 of the benzoylguanidine parent substance;
 or
 R(3) and R(4) are, independently of each other,
 -SR(64), -OR(65), -NHR(66), -NR(67)R(68),
 -CHR(69)R(70),



R(64), R(65), R(66), R(67) and R(69) are, identically or differently,

$-(\text{CH}_2)_y-(\text{CHOH})_z-(\text{CH}_2)_{aa}-(\text{CH}_2\text{OH})_t-\text{R}(71)$ or

$-(\text{CH}_2)_{ab}-\text{O}-(\text{CH}_2-\text{CH}_2\text{O})_{ac}-\text{R}(72)$.

5 R(71) and R(72) are hydrogen or methyl,

u is 1, 2, 3 or 4,

v is zero, 1, 2, 3 or 4,

y, z and aa are, identically or differently,

zero, 1, 2, 3 or 4,

10 t is 1, 2, 3 or 4,

R(68), R(70), R(54) and R(55) are, identically or differently,

hydrogen or (C_1-C_6) -alkyl, or

15 R(69) and R(70) and, respectively, R(54) and R(55)

are, together with the carbon atom carrying them, a

(C_3-C_8) -cycloalkyl;

R(63) is

H, (C_1-C_6) -alkyl, (C_3-C_8) -cycloalkyl or
 $-\text{C}_e\text{H}_{2e}-\text{R}(73)$,

20 e is zero, 1, 2, 3 or 4,

R(56), R(57) and R(73) are, independently,

phenyl,

which is unsubstituted or is substituted by 1-3

substituents from the group F, Cl, CF_3 , methyl,

25 methoxy or $\text{NR}(74)\text{R}(75)$ with R(74) and R(75)

being H or (C_1-C_4) -alkyl,

or R(56), R(57) and R(73) are, independently,

(C_1-C_9) -heteroaryl,

which is unsubstituted or is substituted as

30 phenyl;

R(58), R(59), R(60), R(61) and R(62) are hydrogen or

methyl,

or

R(3) and R(4) are, independently of each other,

35 R(76)- $\text{NH}-\text{SO}_2-$,

R(76) is $\text{R}(77)\text{R}(78)\text{N}-(\text{C}=\text{Y}')$ -,

Y' is oxygen, S or $\text{N}-\text{R}(79)$,

R(77) and R(78) are, identically or differently,

H, (C₁-C₈)-alkyl, (C₃-C₆)-alkenyl,
or C_fH_{2f}-R(80),

f is zero, 1, 2, 3 or 4,

R(80) is (C₅-C₇)-cycloalkyl, or
phenyl

which is unsubstituted or is sub-
stituted by 1-3 substituents from
the group F, Cl, CF₃, methoxy or
(C₁-C₄)-alkyl, or

10 R(77) and R(78) together form 4 or 5 methylene
groups, of which one CH₂ group can be replaced by
oxygen, S, NH, N-CH₃ or N-benzyl, where
R(79) is defined as R(77) or is amidine;

or

15 R(3) and R(4) are, independently of each other,
NR(84)R(85),

R(84) and R(85) are, independently of each other,
H or (C₁-C₄)-alkyl, or, together, can be 4 or 5
methylene groups, of which one CH₂ group can be
20 replaced by oxygen, S, NH, N-CH₃ or N-benzyl,
or of which one or two CH₂ groups can be
replaced by CH-C_{dm}H_{2dm+1},

and the pharmaceutically tolerated salts thereof,

25 where, however, compounds are excepted in which the
radicals R(1) to R(4) and also HA are combined in the
following manner:

R(1)	R(2)	R(3)	R(4)	HA
CON=C(NH ₂)	H	H	Et	O
CON=C(NH ₂)	H	H	Me	O
30 CON=C(NH ₂)	H	H	H	O

Compounds of the formula I are preferred in which:

HA is SO_m, O or NR(5),

m is zero, 1 or 2,

R(5) is hydrogen or methyl,
 one of the two substituents R(1) and R(2) is
 $-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$,
 and whichever is the other is hydrogen, F, Cl, CH_3 , -OH
 5 or $-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$,

R(3) is hydrogen, F, Cl, Br, I, $-\text{C}\equiv\text{N}$, $\text{C}_q-\text{F}_{2q+1}$, R(8)- SO_2 ,
 R(9)R(10)N-CO, R(11)-CO- or R(12)R(13)N- SO_2 -,

where the perfluoroalkyl group is straight-chain
 or branched,

10 q is zero, 1, 2, 3, 4, 5 or 6,

R(8), R(9), R(11) and R(12) are, independently,
 (C_1-C_8) -alkyl, (C_3-C_4) -alkenyl, $-\text{C}_n\text{H}_{2n}-\text{R}(15)$ or
 CF_3 ,

n is zero, 1, 2, 3 or 4,

15 R(15) is (C_3-C_6) -cycloalkyl, or phenyl

which is not substituted or is substi-
 tuted by 1 - 2 substituents from the
 group F, Cl, CF_3 , methyl, methoxy or
 NR(16)R(17), with R(16) and R(17) being H
 20 or methyl,

where R(9), R(11) and R(12) also have the meaning
 of H,

R(10) and R(13) are, independently, H or methyl,

or

25 R(3) is (C_1-C_8) -alkyl or $-\text{C}_{a1}\text{H}_{2a1}\text{R}(18)$,

a_1 is zero, 1 or 2,

R(18) is (C_3-C_6) -cycloalkyl, or phenyl

30 which is not substituted or is substi-
 tuted by 1 - 2 substituents from the
 group F, Cl, CF_3 , methyl, methoxy or
 NR(19)R(20), with R(19) and R(20) being H
 or CH_3 ;

or

35 R(3) is quinolyl, isoquinolyl, pyrrolyl, pyridyl or
 imadazolyl which are linked via C or N and
 which are unsubstituted or are substituted by
 1 - 2 substituents from the group F, Cl, CF_3 ,
 CH_3 , methoxy, hydroxyl, amino, methylamino or
 dimethylamino;

or

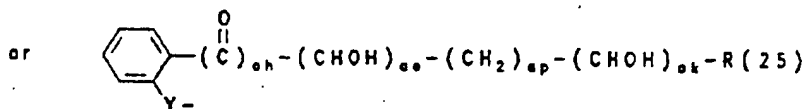
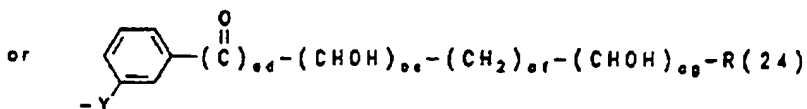
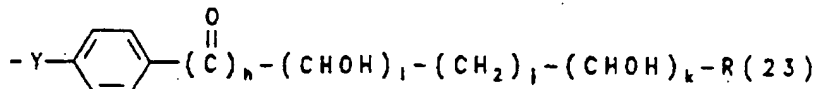
R(3) is $-C\equiv CR(56)$,

R(56) is phenyl,

5

which is unsubstituted or is substituted by 1 - 2 substituents from the group F, Cl, CF_3 , methyl, methoxy or $NR(16)R(17)$, with R(16) and R(17) being H or CH_3 ,

R(4) is



Y is oxygen, -S- or $-NR(22)-$,

10

h, ad and ah are, independently, zero or 1,
i, k, ag, ao and ak are, independently, zero, 1, 2 or 3,
j, aj and ap are, independently, zero or 1,
where, however, in each case,

15

h, i and k are not simultaneously zero,
ad, ae and ag are not simultaneously zero, and
ah, ao and ak are not simultaneously zero,
R(23), R(24), R(25) and R(22) are, independently,
hydrogen or methyl,

20

or

R(4) is hydrogen, F, Cl, Br, CN, (C_1-C_8) -alkyl, C_q-F_{2q+1} ,
 (C_3-C_8) -alkenyl or $-C_gH_{2g}R(26)$,

where the perfluoroalkyl group is straight-chain or branched,

25

q is zero, 1, 2, 3 or 4,
g is zero, 1 or 2,

R(26) is (C₃-C₈)-cycloalkyl, or phenyl
 which is not substituted or is substituted by
 1 - 2 substituents from the group F, Cl, CF₃,
 methyl, methoxy or NR(27)R(28), with R(27) and
 R(28) being H or CH₃,

5

or

R(4) is SR(29), -OR(30), -NR(31)R(32) or
 -CR(33)R(34)R(35);

10

R(29), R(30), R(31) and R(33) are, independently,
 -C_aH_{2a}- (C₁-C₉)-heteroaryl, selected from the group
 consisting of pyrrolyl, imidazolyl, pyrazolyl and
 pyridyl,

15

which is unsubstituted or is substituted
 by 1 - 2 substituents from the group F,
 Cl, CF₃, CH₃, methoxy, hydroxyl, amino,
 methylamino or dimethylamino,
 a is zero or 1,

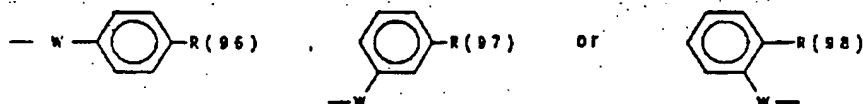
R(32), R(34) and R(35) are, independently of each
 other,

20

hydrogen or CH₃,

or

R(4) is



R(96), R(97) and R(98) are, independently, pyrrolyl,
 imidazolyl, pyrazolyl or pyridyl,

25

which, in each case, is unsubstituted or is
 substituted by 1 - 2 radicals from the group
 comprising
 F, Cl, CF₃, CH₃, methoxy, dimethylamino or
 benzyl,

30

W is oxygen, S or NR(36)-,

R(36) is H or methyl,

or

R(4) is R(37)-SO_{cm} or R(38)R(39)N-SO₂-,

R(37) is (C₁-C₆)-alkyl, CF₃, (C₃-C₄)-alkenyl or

$-C_sH_{2s}-R(40)$,

s is zero or 1,

R(40) is (C_3-C_6) -cycloalkyl, or phenyl

5

which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF_3 , methyl, methoxy or NR(41)R(42), with R(41) and R(42) being H or CH_3 ,

R(38) is H, (C_1-C_4) -alkyl, CF_3 , (C_3-C_4) -alkenyl or $-C_wH_{2w}-R(43)$,

10

w is zero or 1

R(43) is (C_3-C_8) -cycloalkyl, or phenyl

15

which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF_3 , methyl, methoxy or NR(44)R(45), with R(44) and R(45) being H, (C_1-C_4) -alkyl or CH_3 ,

R(39) is H or CH_3 ,

20

where R(38) and R(39) can together be 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, S, NH, N- CH_3 or N-benzyl;

or

R(4) is R(46)X(1)-,

25

X(1) is oxygen, S, NR(47), $(C=O)A-$ or NR(48)C=MN^(*)R(49)-,

M is oxygen,

A is oxygen or NR(50),

30

R(46) is (C_1-C_6) -alkyl, (C_3-C_4) -alkenyl, $(CH_2)_bC_dF_{2d+1}$ or $-C_xH_{2x}-R(51)$.

b is zero or 1,

d is 1, 2, 3, 4, 5, 6 or 7,

x is zero or 1,

35

R(51) is (C_3-C_8) -cycloalkyl, or phenyl

which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF_3 , methyl, methoxy or NR(52)R(53); with R(52) and R(53) being H or CH_3 ,

R(47), R(48) and R(50)

are hydrogen or (C₁-C₄)-alkyl,

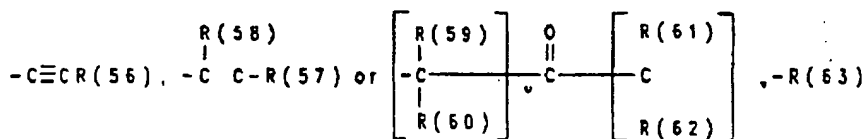
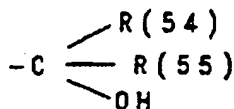
R(49) is defined as R(46), where

5 R(46) and R(47) and, respectively, R(46) and R(48) can together be 4 or 5 methylene groups; of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl, where A and N^(*) are bonded to the phenyl nucleus of the benzoylguanidine parent substance;

10

or

R(4) is -SR(64), -OR(65), -NHR(66), -NR(67)R(68),
-CHR(69)R(70),



15 R(64), R(65), R(66), R(67) and R(69) are, identically or differently,

-(CH₂)_y-(CHOH)_z-(CH₂)_{aa}-(CH₂OH)_t-R(71) or
-(CH₂)_{ab}-O-(CH₂-CH₂O)_{ac}-R(72),

R(71) and R(72) are hydrogen or methyl,

u is 1 or 2,

20 v is zero, 1 or 2,

y, z and aa are, identically or differently,

zero, 1 or 2,

t is 1, 2 or 3,

25 R(68), R(70), R(54) and R(55) are, identically or differently,

hydrogen or CH₃,

or

R(69) and R(70) and, respectively, R(54) and R(55) are, together with the carbon atom carrying them, a

(C₃-C₆)-cycloalkyl;

R(63) is

H, (C₁-C₄)-alkyl, (C₃-C₆)-cycloalkyl or
-C_eH_{2e}-R(73),

5 e is zero, 1 or 2,

R(56), R(57) and R(73) are, independently,
phenyl

10 which is unsubstituted or is substituted
by 1 - 2 substituents from the group F,
Cl, CF₃, methyl, methoxy or NR(74)R(75),
with R(74) and R(75) being H or CH₃,

or

R(56), R(57) and R(73) are, independently,

15 (C₁-C₉)-heteroaryl, selected from the group consist-
ing of pyrrolyl, imidazolyl, pyrazolyl and pyridyl,
which is unsubstituted or is substituted
as phenyl;

R(58), R(59), R(60), R(61) and R(62)
are hydrogen or methyl,

20 or

R(4) is R(76)-NH-SO₂-,

R(76) is R(77)R(78)N-(C=Y')-,

Y' is oxygen, S or N-R(79),

25 R(77) and R(78) are, identically or
differently,

H, (C₁-C₄)-alkyl, (C₃-C₄)-alkenyl or
-C_fH_{2f}-R(80),

f is zero or 1,

R(80) is

30 (C₅-C₇)-cycloalkyl, or phenyl

which is unsubstituted or is
substituted by 1 - 2 substi-
tuents from the group F, Cl,
CF₃, methoxy or CH₃, or

35 R(77) and R(78) together form 4 or 5
methylene groups, of which one CH₂ group
can be replaced by oxygen, S, NH, N-CH₃ or
N-benzyl, where

R(79) is defined as R(77),

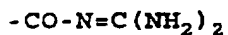
or

R(4) is NR(84)R(85),

5 R(84) and R(85) are, independently of each other,
H or (C₁-C₄)-alkyl, or together form 4 or 5
methylene groups, of which one CH₂ group can be
replaced by oxygen, S, NH, N-CH₃ or N-benzyl,
or of which one or two CH₂ groups can be
replaced by CH-CH₃.

10 Compounds of the formula I are particularly preferred in
which:

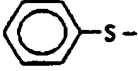
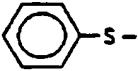


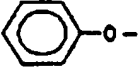



R(1) is

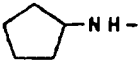
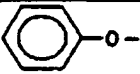
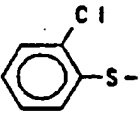
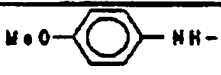
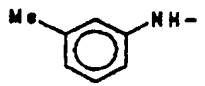
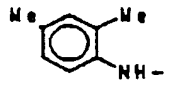

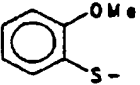
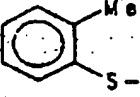
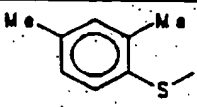


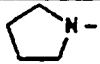
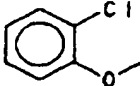

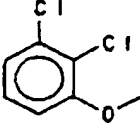

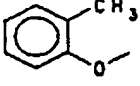

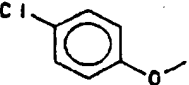
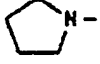
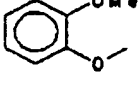

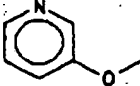
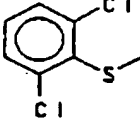
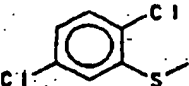
HA is


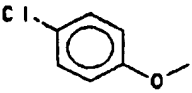
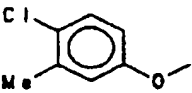
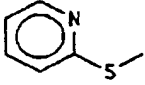
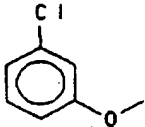

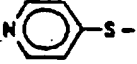


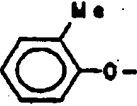
S, O, NH or NCH₃,

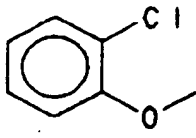

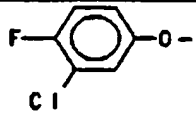


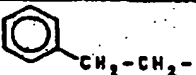
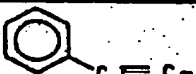
15 and the radicals R(2) to R(4) are combined as follows:



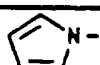

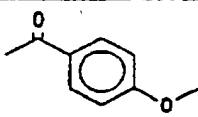
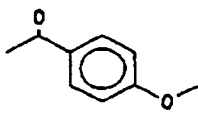


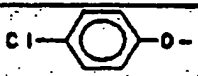
R(2)	R(3)	R(4)
H	n-BuNH-	Cl
H	H ₂ NSO ₂ -	
H	MeSO ₂	
H		Me
H		
H		Me
H		Cl
H		MeSO ₂ -


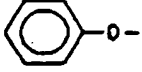



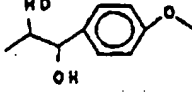

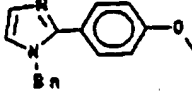
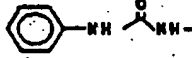
H	MeSO ₂	NH ₂
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	Cl ⁻	
H	MeSO ₂ ⁻	(CH ₃) ₂ -CHCH ₂ -O-
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	

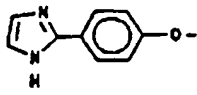
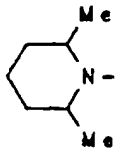
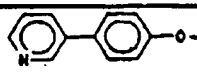
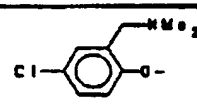
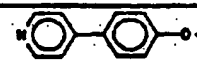
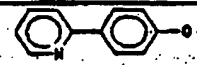
H		
H		
H		
H		
H		
H		
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
Me	Me	H
H	MeSO ₂ ⁻	i-Pr
H	CF ₃	H

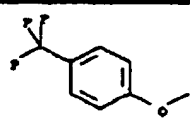
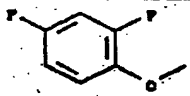
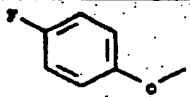
H		Cl
H	MeSO ₂ -	MeNH-
H	MeSO ₂ -	Et ₂ N-
H	t-Bu	OH
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	2-Naphthyl
H	MeSO ₂ -	
H		Me
H		
H	Cl	Et ₂ N-
H	Me ₂ N-	H

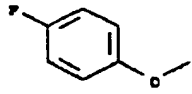
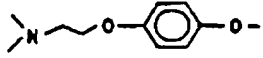
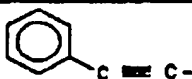

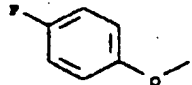
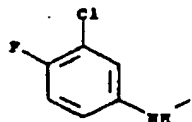
H	MeSO ₂ ⁻	
H	Br	NH ₂
H	Cl	H
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	CF ₃	CF ₃
H	Me	Me
H	I	CF ₃
H	Me	H
H	H	t-Bu
H	MeSO ₂ ⁻	
H	Me	Cl
H	Br	Me
H	Cl	MeO-
H	MeCO-	
H	Br	Br
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
NH ₂	Br	Me

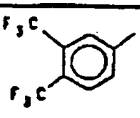
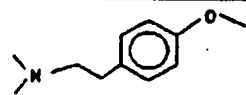
H	Me ₂ N-	t-Bu
H	MeSO ₂ -	HO-  -
H	 -	H
H	 -	MeO-
H	Me	Br
H	Cl	F
H	t-Bu	H
NH ₂	Cl	H
H	 -	Me ₂ N
H	Me ₂ N	Cl
H	MeSO ₂ -	7-Isoquinolinoxy
H	MeSO ₂ -	6-quinolinoxy
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	(CH ₃) ₂ CH-CH ₂ -
H	MeSO ₂ -	
H	Me ₂ N-	 -
H	Me ₂ N-	Cl-  -
H	Me	Me ₂ N-

H		
H	Me	
H	Cl	i-Pr
H		i-Pr
H	MeSO ₂ ⁻	5-quinolinoxy
H		CF ₃
H	i-Pr	MeSO ₂ ⁻
H	i-Pr	CF ₃
H	H	i-Pr
NH ₂	Br	Br
H	MeSO ₂ ⁻	
H		MeSO ₂ ⁻
H	MeSO ₂ ⁻	
H	Cl	
H	Me ₂ N	i-Pr
H	MeHN-	i-Pr
H	Cl	Cl
H	Me	H ₂ N-
H	Cl	H ₂ N

H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	Me ₂ N-	i-Pr
CF ₃	H	CF ₃
H	Br	Me
H	Me	Cl
H	Me ₂ N	Me
H	CF ₃	MeHN-
H	CH ₃ CO-	(CH ₃) ₂ CH-CH ₂
H	MeSO ₂ ⁻	
H	CF ₃ -O-	H
H	Me	Me ₂ N
H	Cl	Me ₂ N-
H	MeSO ₂ ⁻	
H	CH ₃ CO-	i-Pr
H	Br	BnO-
H	CF ₃	Br
H	i-Pr	MeO-
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	

H	MeO-	t-Bu
H	Br	i-Pr
CF ₃	H	H
H	CF ₃	F
H	Ph	CF ₃
H	CF ₃	1-Imidazolyl
H	MeCO-	t-Butylmethyl
H	Br	F
H	Br	MeO-
H	CF ₃	PhO-
H	CF ₃	Cyclopentyl
H	MeSO ₂ -	Cyclobutyl
H	Me	CF ₃
H	MeSO ₂ -	
H	OH	t-Butyl
H	Cl	OMe
H	CF ₃	i-Pr
F	CF ₃	H
F	H	CF ₃
H	t-Butyl	OMe
H	MeCO-	
H	MeCO-	
H	t-Butyl	i-Butyl
H	CF ₃ CF ₂ -	i-Propyl

H	CF ₃ -SO ₂ -	
Cl	CF ₃	H
Cl	H	CF ₃
H	H	Perfluoro-i-propyl
H	H	H
H	MeSO ₂ -	
H	H	Perfluoro-n-propyl
H	CF ₃	
H	CF ₃	
H	CF ₃	
H	F	CF ₃
H	MeSO ₂ -	
H	t-Butyl	i-Propyl
H	t-Butyl	n-Butyl
H	i-Propyl	F
H	i-Butyl	F
H	Cl	1-Imidazolyl
H	H	CF ₃ -CF ₂ -
H	H	CF ₃

H	H	
H	MeSO ₂	
H	CF ₃ SO ₂	i-propyl

(C₁-C₉)-Heteroaryl is understood to mean, in particular, radicals which are derived from phenyl or naphthyl and in which one or more CH groups is/are replaced by N, and/or in which at least two adjacent CH groups are replaced
 5 (with the formation of a five-membered aromatic ring) by S, NH or O. In addition, one or both atoms of the condensation site of bicyclic radicals may also be N atoms (as in indoliziny).

Heteroaryl is, in particular, furanyl, thienyl, pyrrolyl,
 10 imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, quinoxaliny, quinazoliny and cinnoliny.

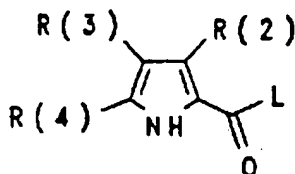
15 If one of the substituents R(1) to R(5) contains one or more centers of asymmetry, these latter can be either in the S or R configuration. The compounds may be present as optical isomers, as diastereomers, as racemates, or as mixtures thereof.

20 The designated alkyl radicals may be either straight-chain or branched.

The invention furthermore relates to a process for

preparing compounds I, wherein compounds

of the formula II



in which L is a leaving group which can readily be substituted nucleophilically, are reacted with guanidine.

- 5 The activated acid derivatives of the formula II in which L is an alkoxy, preferably a methoxy, group, a phenoxy group, a phenylthio, methylthio or 2-pyridylthio group, or a nitrogen heterocycle, preferably 1-imidazolyl, are advantageously obtained, in a manner known per se, from
- 10 the underlying carbonyl chlorides (formula II, L = Cl), which for their part, can be prepared, once again in a manner known per se, from the underlying carboxylic acids (formula II, L = OH), for example using thionyl chloride. In addition to the carbonyl chlorides of the formula II
- 15 (L = Cl), other activated acid derivatives of the formula II can also be prepared, in a manner known per se, directly from the underlying heteroarylcarboxylic acid derivatives (formula II, L = OH) as can, for example, the methyl esters of the formula II with L = OCH₃ by treat-
- 20 ment with gaseous HCl in methanol, the imidazolides of the formula II by treatment with carbonyldiimidazole [L = 1-imidazolyl, Staab, Angew. Chem. Int. Ed. Engl. 1, 351-367 (1962)], the mixed anhydrides II with Cl-COOC₂H₅ or tosyl chloride in the presence of triethylamine in an
- 25 inert solvent, in addition to which there is also the activation of heteroarylcarboxylic acids with dicyclohexylcarbodiimide (DCC) or with O-[(cyano(ethoxycarbonyl)methylene)amino]-1,1,3,3-tetramethyluronium tetrafluoroborate ("TOTU") [Proceedings of the 21st
- 30 European Peptide Symposium, Peptides 1990, Editors

E. Giralt and D. Andreu, *Escom, Leiden, 1991*]. A series of suitable methods for preparing activated carboxylic acid derivatives of the formula II is given, with citation of the source literature, on p. 350 in J. March, 5 *Advanced Organic Chemistry, Third Edition (John Wiley & Sons, 1985)*.

An activated carboxylic acid derivative of the formula I is reacted with guanidine, in a manner known per se, in a protic or aprotic polar, but nevertheless inert, 10 organic solvent. In this context, methanol, isopropanol or THF, at a temperature of from 20°C up to the boiling temperature of these solvents, have proved of value when reacting the methyl heteroarylcarboxylates (II, L = OMe) with guanidine. Most of the reactions of compounds II 15 with salt-free guanidine were advantageously carried out in inert solvents such as THF, dimethoxyethane, dioxane or isopropanol. However, water can also be used as the solvent.

When L is Cl, the reaction is advantageously carried out 20 with the addition of an acid-capturing agent, for example in the form of excess guanidine, for binding the hydrohalic acid.

Some of the underlying heteroaryl carboxylic acid derivatives of the formula II are known and described in the 25 literature. The unknown compounds of the formula II may be prepared by methods which are known from the literature, by, for example, converting 5-halo-4-chlorosulfonylbenzoic acids, with ammonia or amines, into 4-aminosulfonyl-5-halo-heteroarylcarboxylic acids, or, with 30 a weak reducing agent, such as sodium bisulfite, and subsequent alkylation, into 4-alkylsulfonyl-5-halo-heteroarylcarboxylic acids, and transforming them, by one of the above-described process variants, into compounds I according to the invention.

35 The introduction of substituted sulfur nucleophiles,

oxygen nucleophiles or nitrogen nucleophiles is achieved using methods, which are known from the literature, for nucleophilic substitution in an aromatic compound. In this substitution, halides and trifluoromethanesulfonates
5 have proved to be of value as leaving groups. The reaction is advantageously carried out in a dipolar aprotic solvent, such as, for example, DMF or TMU, at a temperature of between 0°C and the boiling point of the solvent, preferably between 80°C and the boiling point of the
10 solvent. An alkali metal salt or alkaline earth metal salt having an anion of high basicity and low nucleophilicity, such as, for example, K_2CO_3 , is advantageously used as acid-capturing agent.

The introduction of the alkyl or aryl substituents is
15 achieved by the methods, which are known from the literature, of palladium-mediated cross-coupling of aryl halides with, for example, organozinc compounds, organostannanes, organoboronic acids or organoboranes.

In general, heteroaroylguanidines I are weak bases and
20 can bind acid with the formation of salts. Suitable acid addition salts are the salts of all pharmacologically tolerated acids, for example halides, in particular hydrochlorides, lactates, sulfates, citrates, tartrates, acetates, phosphates, methylsulfonates and p-toluenesul-
25 fonates.

It was surprising that, while the compounds according to the invention do not exhibit any undesirable and disadvantageous salidiuretic properties, they do exhibit very good antiarrhythmic properties, as are important for
30 treating diseases which occur, for example, in association with symptoms of oxygen deficiency. As a consequence of their pharmacological properties, the compounds are outstandingly suitable for use as antiarrhythmic pharmaceuticals possessing a cardioprotective
35 component for the prophylaxis and treatment of infarction and for the treatment of angina pectoris, in connection

with which they also inhibit or strongly reduce, in a preventive manner, the pathophysiological processes associated with the genesis of ischemically induced damage, in particular associated with the elicitation of ischemically induced cardiac arrhythmias. On account of their protective effects against pathological hypoxic and ischemic situations, the compounds of the formula I according to the invention can, as a consequence of inhibiting the cellular Na^+/H^+ exchange mechanism, be used as pharmaceuticals for treating all acute or chronic damage elicited by ischemia, or diseases induced primarily or secondarily thereby. This is the case with regard to their use as pharmaceuticals for surgical interventions, for example in organ transplantations, where the compounds can be used both for protecting the organs in the donor prior to and during removal, for protecting organs which have been removed, for example when they are being treated with or stored in physiological bathing fluids, and when transferring the organs into the recipient. The compounds are likewise valuable protective pharmaceuticals to be used when carrying out angioplastic surgical interventions, for example on the heart or on peripheral vessels. In conformity with their ability to protect against ischemically induced damage, the compounds are also suitable for use as pharmaceuticals for the treatment of ischemias of the nervous system, in particular of the CNS, in connection with which they are suitable, for example, for the treatment of stroke or cerebral edema. Over and above this, the compounds of the formula I according to the invention are also suitable for use in the treatment of forms of shock, such as, for example, allergic, cardiogenic, hypovolemic and bacterial shock.

In addition to this, the compounds of the formula I according to the invention are notable for their strong inhibitory effect on the proliferation of cells, for example the proliferation of fibroblast cells and the proliferation of the smooth muscle cells of the blood

- vessels. For this reason, the compounds of the formula I are valuable therapeutic agents for use in diseases in which cell proliferation represents a primary or secondary cause and may, therefore, be used as antiathero-
- 5 sclerotic agents, and as agents against diabetic late complications, cancerous diseases, fibrotic diseases such as pulmonary fibrosis, hepatic fibrosis or renal fibrosis, and against organ hypertrophies or hyperplasias, in particular hyperplasia or hypertrophy of the prostate.
- 10 The compounds according to the invention are efficient inhibitors of the cellular sodium/proton antiporter (Na^+/H^+ exchanger), which, in numerous diseases (essential hypertension, atherosclerosis, diabetes, etc.), is also elevated in those cells which are readily accessible
- 15 to measurement, such as, for example, erythrocytes, thrombocytes or leucocytes. The compounds according to the invention therefore represent outstanding and simple scientific tools, for example in their use as diagnostic agents for defining and differentiating particular forms
- 20 of hypertension and also of atherosclerosis, diabetes, proliferative diseases, etc. In addition to this, the compounds of the formula I can suitably be used in preventive therapy for preventing the genesis of high blood pressure, for example of essential hypertension.
- 25 The compounds according to the invention exhibit a solubility in water which is significantly superior to that of the known compounds. For this reason, their suitability for i.v. administration is considerably greater.
- 30 In this context, pharmaceuticals which contain a compound I may be administered orally, parenterally, intravenously or rectally, or by inhalation, the preferred route of administration depending on the given features of the disease. In this context, the compounds I may be used
- 35 either alone or together with pharmaceutical auxiliary substances, both in veterinary and in human medicine.

Owing to his specialist knowledge, the person skilled in the art is familiar with those auxiliary substances which are suitable for the desired pharmaceutical formulation. Antioxidants, dispersants, emulsifiers, defoamers, taste corrigents, preservatives, solubilizers or dyes, for example, can be used in addition to solvents, gel formers, suppository bases, tablet auxiliaries and other active compound excipients.

For a form for oral use, the active compounds are mixed with the additives, such as carrier substances, stabilizers or inert diluents, which are suitable for the purpose, and brought by the customary methods into the forms, such as tablets, coated tablets, hard gelatin capsules, or aqueous, alcoholic or oily solutions, which are suitable for administration. Gum arabic, magnesium oxide, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch, can, for example, be used as inert excipients. In this context, the preparation can be effected either as a dry granulate or as a wet granulate. Vegetable or animal oils, for example, such as sunflower oil or cod-liver oil, are suitable for use as oily excipients or as solvents.

For subcutaneous or intravenous administration, the active compounds are brought into solution, suspension or emulsion, if desired using the substances, such as solubilizers, emulsifiers or other auxiliary substances, which are customary for the purpose. Examples of suitable solvents are: water, physiological sodium chloride solution or alcohols, for example ethanol, propanol or glycerol, as well as sugar solutions, such as glucose or mannitol solutions, or else a mixture of the different solvents mentioned.

Solutions, suspensions or emulsions of the active compound of the formula I in a pharmaceutically harmless solvent, such as, in particular, ethanol or water, or in a mixture of such solvents, represent examples of

suitable pharmaceutical formulations for administration in the form of aerosols or sprays. As required, the formulation can also contain additional pharmaceutical auxiliary substances such as surfactants, emulsifiers and stabilizers, as well as a propellant gas. Such a preparation customarily contains the active compound in a concentration of from about 0.1 to 10, in particular of from about 0.3 to 3, % by weight.

The dosage of the active compound of the formula I to be administered, and the frequency of administration, depend on the strength and duration of the effect of the compounds used; additionally also on the nature and severity of the disease to be treated and on the sex, age, weight and individual responsiveness of the mammalian subject to be treated.

On average, the daily dose of a compound of the formula I is, for a patient of approximately 75 kg in weight, at least 0.001 mg, preferably 0.01 mg to 10 mg, preferably 1 mg. In acute manifestations of the disease, for example immediately after suffering a cardiac infarction, even greater and, in particular, more frequent dosages may also be necessary, for example up to 4 individual doses per day. In the case of i.v. use in particular, for example in an infarction patient in intensive care, up to 100 mg per day may be necessary.

The novel compounds of the formula I which are listed below, and their physiologically tolerated salts, can be prepared in analogy with the instructions given in the exemplary embodiments:

30 List of abbreviations:

MeOH	methanol
DMF	N,N-dimethylformamide
TMU	N,N,N',N'-tetramethylurea
NBS	N-bromosuccinimide

	AIBN	α, α -azobis(isobutyronitrile)
	EI	electron impact
	DCI	desorption chemical ionisation
	RT	room temperature
5	EA	ethyl acetate (EtOAc)
	DIP	diisopropyl ether
	MTB	methyl tert-butyl ether
	mp	melting point
	HEP	n-heptane
10	DME	dimethoxyethane
	FAB	fast atom bombardment
	CH ₂ Cl ₂	dichloromethane
	THF	tetrahydrofuran
	eq	equivalent
15	ES	electrostatic spray ionization
	Me	methyl
	Et	ethyl
	Bn	benzyl
	CNS	central nervous system
20	brine	saturated aqueous solution of NaCl

Experimental Section

Example 1

5-Heptafluoroisopropyl-1-methylpyrrole-2-carboguanidide

- a) Methyl 5-heptafluoroisopropyl-1-methylpyrrole-2-carboxylate
- 25
1.1 g of methyl 1-methylpyrrole-2-carboxylate, 1.7 ml of perfluorocisopropyl iodide and 1.3 g of FeSO₄ · 7 H₂O are initially introduced in 80 ml of DMSO, and 4.1 ml of H₂O₂ (35%) are slowly added dropwise at RT. The mixture is
- 30
stirred at RT for 1.5 h and then extracted 3 x with 200 ml of MTB on each occasion, and the organic phase is additionally washed 1 x with 100 ml of water and 2 x with 100 ml of brine. Drying takes place over Na₂SO₄ and the solvent is removed in vacuo. Chromatography using EA/HEP
- 35
1/4 gives 310 mg of a colorless oil.
- R_f (EA/HEP 1/4) = 0.62 MS (DCI): 308 (M + H)⁺

b) 5-Heptafluoroisopropyl-1-methylpyrrole-2-carbo-
guanidide

310 mg of methyl 5-heptafluoroisopropyl-1-methylpyrrole-
2-carboxylate and 295 mg of guanidine are boiled under
5 reflux, for 4 h, in 5 ml of anhydrous isopropanol. The
solvent is removed in vacuo and the residue is chromato-
graphed using EA. 123 mg of a colorless oil are obtained.
R_f(EA) = 0.26 MS (ES): 335 (M + H)⁺
Conversion into the hydrochloride yields white crystals,
10 mp 165°C

The title compounds in Examples 2 - 5 are synthesized in
analogy with Example 1:

Example 2

5-Heptafluoro-n-propyl-1-methylpyrrole-2-carboguanidide
15 R_f(EA) = 0.20 MS (ES): 335 (M + H)⁺
mp (hydrochloride): 207°C

Example 3

5-Pentafluoroethyl-1-methylpyrrole-2-carboguanidide
R_f(EA) = 0.16 MS (DCI) : 285 (M + H)⁺
20 mp (hydrochloride): 210°C

Example 4

5-Trifluoromethyl-1-methylpyrrole-2-carboguanidide
R_f(EA) = 0.16 MS (DCI): 235 (M + H)⁺
mp (hydrochloride): 230°C

25 Example 5

1-Methylpyrrole-2-carboguanidide
R_f(EA/MeOH 10:1) = 0.13 MS(ES): 167 (M + H)⁺
mp (hydrochloride): 255°C

Example 6

30 5-Isopropyl-4-methylsulfonylthiophene-2-carboguanidide
a) 5-bromothiophene-2-carboxylic acid
10 g of thiophene-2-carboxylic acid are dissolved in

100 ml of acetic acid and 100 ml of water, and a solution of 4 ml of bromine in 50 ml of acetic acid and 50 ml of water is added dropwise, at 0°C, over a period of one hour. The mixture is subsequently stirred at 0°C for 1 h and the product is then filtered off with suction and recrystallized from water. 4.8 g of colorless crystals are obtained, mp 140°C

R_f (MTB 2% HOAc) = 0.54 MS(DCI): 207 (M + H)⁺

b) 5-Bromo-4-chlorosulfonylthiophene-2-carboxylic acid
37 g of 5-bromothiophene-2-carboxylic acid are dissolved, at RT, in 133 ml of chlorosulfonic acid, and this mixture is stirred at 100°C for 45 min. The mixture is subsequently poured onto 1 kg of ice and the product is filtered off with suction. 53 g of a colorless solid are obtained, mp 96°C

R_f (MTB 2% HOAc) = 0.3 MS(DCI): 305 (M + H)⁺

c) 5-Bromo-4-hydroxysulfinylthiophene-2-carboxylic acid
27.5 g of sodium sulfite are dissolved in 300 ml of water, and a total of 35 g of 5-bromo-4-chlorosulfonylthiophene-2-carboxylic acid is added, in portions, at 70°C, with a pH of 9 - 11 being maintained using 10 N NaOH. The mixture is subsequently stirred at 70°C for 2 h and then adjusted to pH = 1 with HCl, after which the product is filtered off with suction. 41 g of colorless crystals are obtained.
mp 195°C (decomposition)

d) 5-Bromo-4-hydroxysulfinylthiophene-2-carboxylic acid, disodium salt
41 g of 5-bromo-4-hydroxysulfinylthiophene-2-carboxylic acid are suspended in 150 ml of water, and 90 ml of 2 N NaOH are added (pH = 10). The water is removed in vacuo, the residue is stirred up in 1 l of acetone, and the product is filtered off with suction. 46 g are obtained of a colorless, amorphous solid, which is immediately subjected to further reaction.

e) Methyl 5-bromo-4-methylsulfonylthiophene-2-carboxylate
46 g of the title compound 6 d) are suspended in 150 ml
of DMF, and 32 ml of methyl iodide are added. The mixture
is stirred at 50°C for 5 h and then poured onto 1 l of
5 water; the product is filtered off with suction. 35 g of
a colorless solid are obtained, mp 135°C
 $R_f(\text{DIP}) = 0.20$ $\text{MS}(\text{DCI}): 299 (\text{M} + \text{H})^+$

f) Methyl 5-isopropyl-4-methylsulfonylthiophene-2-carboxylate
10 30 ml of a 2 M solution of isopropylmagnesium chloride in
THF are added to 140 ml of a 0.5 M solution of zinc
chloride in THF. The mixture is stirred at 50°C for 5 h
and the resulting isopropylzinc derivative undergoes
further use as solution A. 6 g of methyl 5-bromo-4-
15 methylsulfonylthiophene-2-carboxylate, 0.6 g of [1,1'-
bis(diphenylphosphino)ferrocene]Pd(II)Cl₂ x CH₂Cl₂ and
180 mg of CuI are stirred, at RT for 10 min, in 100 ml of
anhydrous THF, and solution A is subsequently added
dropwise. The mixture is subsequently stirred at RT for
20 18 h, and the solvent is then removed in vacuo. The
residue is suspended in 200 ml of a saturated aqueous
solution of NaHSO₄, and this suspension is extracted 3 x
with 200 ml of EA on each occasion. Drying takes place
over Na₂SO₄, the solvent is removed in vacuo, and the
25 residue is chromatographed using once in each case, DIP
and EA/HEP 1:3. 1.7 g of a colorless oil are obtained.
 $R_f(\text{DIP}) = 0.29$ $R_f(\text{EA/HEP } 1:3) = 0.32$
 $\text{MS}(\text{DCI}) : 263 (\text{M} + \text{H})^+$

g) 5-Isopropyl-4-methylsulfonylthiophene-2-carboguanidide
30 700 mg of methyl 5-isopropyl-4-methylsulfonylthiophene-2-
carboxylate and 790 mg of guanidine are dissolved in 5 ml
of anhydrous isopropanol, and this mixture is boiled
under reflux for 1 h. The solvent is removed in vacuo and
80 ml of water are added; the mixture is adjusted to
35 pH = 2 with aqueous HCl, and the product is filtered off.
The precipitate is dissolved in 50 ml of a saturated
aqueous solution of Na₂CO₃, and this solution is

extracted 3 x with 50 ml of EA on each occasion. The organic phase is dried over Na_2SO_4 , and the solvent is removed in vacuo. 850 mg of an amorphous solid are obtained.

- 5 $R_f(\text{MeOH/EA } 1:10) = 0.41$ MS(ES): 290 (M + H)⁺
mp (hydrochloride): 267°C
mp (methanesulfonate) : 128°C

The title compounds of Examples 7, 8 and 10 were synthesized in analogy with Example 6 g):

10 Example 7

5-Methylthiophene-2-carboguanidide

mp (hydrochloride) : 236°C MS(DCI) : 184 (M + H)⁺

Example 8

4,5-Dibromothiophene-2-carboguanidide

- 15 mp (hydrochloride) : 268°C MS(DCI) : 326 (M + H)⁺

Example 9

4-Isopropyl-5-methylsulfonylthiophene-2-carboguanidide

a) 4-Bromo-5-methylthiothiophene-2-carboxylic acid

- 20 25 g of 4,5-dibromothiophenecarboxylic acid, 12.2 g of NaSCH_3 and 60 g of K_2CO_3 are stirred, at 120°C for 5 h, in 1 l of DMF. This mixture is then poured onto 3 l of water, and the pH of the resulting mixture is adjusted to 1 with HCl; the product is filtered off with suction and used for further reaction without purification.

- 25 Yield: 14 g of amorphous powder.

$R_f(\text{DIP } 2\% \text{ HOAc}) = 0.46$

b) 4-Bromo-5-methylsulfonylthiophene-2-carboxylic acid

- 30 14 g of the methylthio compound 9 a) are dissolved in 500 ml of CH_2Cl_2 , and 41 g of m-chloroperbenzoic acid are then added in portions. The mixture is stirred at RT for 1.5 h, and the solvent is then removed in vacuo and the product is esterified without purification.

$R_f(\text{DIP } 2\% \text{ HOAc}) = 0.10$

c) Methyl 4-bromo-5-methylsulfonylthiophene-2-carboxylate
50 ml of SOCl_2 are added to the whole of the crude
product from Example 9 b) in 200 ml of MeOH, and this
mixture is boiled under reflux for 5 h. Excess SOCl_2 and
5 the solvent are removed in vacuo and the residue is
chromatographed using DIP. 11 g of a colorless oil are
obtained.

$R_f(\text{DIP}) = 0.28$ MS(DCI) : 299 (M + H)⁺

d) Methyl 4-isopropyl-5-methylsulfonylthiophene-2-car-
10 boxylate

30 ml of a 2 M solution of isopropylmagnesium chloride in
diethyl ether are added dropwise to a 1 M solution of
 ZnCl_2 in diethyl ether, and this mixture is boiled under
reflux for 6 h. (Solution A)

15 6 g of the bromide 9 c), 588 mg of [1,1-bis(diphenyl-
phosphino)ferrocene]Pd(II) Cl_2 and 183 mg of CuI are
stirred, at RT for 10 min, in 100 ml of THF, and solution
A is then added to this mixture. The resulting mixture is
stirred at RT for 19 h, and 200 ml of EA are then added;
20 the resulting mixture is washed 1 x with 200 ml of water
and 1 x with 200 ml of brine. The solvent is removed in
vacuo and the residue is chromatographed using EA/HEP
1:2.

2 g of a colorless oil are obtained.

25 $R_f(\text{EA/HEP 1:2}) = 0.25$ MS(DCI) : 263 (M + H)⁺

e) 4-Isopropyl-5-methylsulfonylthiophene-2-carboguanidide
1 g of the methyl ester 9 d) is reacted with 1.1 g of
guanidine in analogy with Example 6 g). 900 mg of an
amorphous powder are obtained.

30 $R_f(\text{EA/MeOH 10:1}) = 0.41$ MS(ES) : 290 (M + H)⁺

The compound is converted into the methanesulfonate,
mp = 210°C

Example 10

3-Methylthiophene-2-carboguanidide

mp (hydrochloride) : 232°C

MS(DCI) : 184 (M + H)⁺

Pharmacological data:

Inhibition of the Na⁺/H⁺ exchanger of rabbit erythrocytes

5 New Zealand White rabbits (Ivanovas) were given a standard diet containing 2% cholesterol for six weeks in order to activate Na⁺/H⁺ exchange and thus to be able to use flame photometry to determine the Na⁺ influx into the erythrocytes via Na⁺/H⁺ exchange. The blood was removed from the aural arteries and rendered incoagulable by the
10 addition of 25 IU of potassium heparin. One part of each sample was used for the duplicate determination of the hematocrit by centrifugation. Aliquots of in each case 100 μl were employed for measuring the initial content of Na⁺ in the erythrocytes.

15 In order to determine the amiloride-sensitive sodium influx, 100 μl of each blood sample were in each case incubated, at pH 7.4 and 37°C, in 5 ml of a hyperosmolar salt/sucrose medium (mmol/l: 140 NaCl, 3 KCl, 150 sucrose, 0.1 ouabain, 20 tris(hydroxymethyl)aminomethane).
20 The erythrocytes were then washed three times with ice cold MgCl₂/ouabain solution (mmol/l: 112 MgCl₂, 0.1 ouabain) and hemolyzed in 2.0 ml of distilled water. The intracellular content of sodium was determined by flame photometry.

25 The nett influx of Na⁺ was calculated from the difference between the initial sodium values and the sodium content of the erythrocytes following incubation. The amiloride-inhibitable sodium influx was given by the difference in the sodium content of the erythrocytes following incubation with and without 3 x 10⁻⁴ mol/l amiloride. The same
30 procedure was also used in the case of the compounds according to the invention.

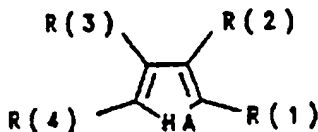
R sults

Inhibition of the Na⁺/H⁺-exchanger:

Example	IC ₅₀ [μmol/l]
1	0.3
2	1.0
3	0.3
4	0.2
5	5.0
6	0.5
7	3
8	0.5

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A heteroaroylguanidine of the formula I



in which:

HA is SO_m , O, or $\text{NR}(5)$,

5 m is zero, 1 or 2,

R(5) is hydrogen, $(\text{C}_1\text{-C}_8)$ -alkyl or $-\text{C}_{am}\text{H}_{2am}\text{R}(81)$,

am is zero, 1 or 2

R(81) is $(\text{C}_3\text{-C}_8)$ -cycloalkyl, or phenyl

10 which is not substituted or is substituted by 1-3 substituents from the group F, Cl, CF_3 , methyl, methoxy or $\text{NR}(82)\text{R}(83)$, with R(82) and R(83) being H or CH_3 ;

or

15 R(81) is $(\text{C}_1\text{-C}_9)$ -heteroaryl which is linked via C or N and which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF_3 , CH_3 , methoxy, hydroxyl, amino, methyl-amino, or dimethylamino;

20 one of the two substituents R(1) and R(2)

is $-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$,

and whichever is the other is

25 hydrogen, F, Cl, Br, I, $(\text{C}_1\text{-C}_3)$ -alkyl, $-\text{OR}(6)$, $\text{C}_r\text{F}_{2r+1}$, $-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$ or $-\text{NR}(6)\text{R}(7)$,

R(6) and R(7) are, independently, hydrogen or $(\text{C}_1\text{-C}_3)$ -alkyl,

r is 1, 2, 3 or 4,

30 R(3) and R(4) are, independently of each other,

hydrogen, F, Cl, Br, I, $-\text{C}\equiv\text{N}$, $\text{X}-(\text{CH}_2)_p-(\text{C}_q-\text{F}_{2q+1})$, $\text{R}(8)-\text{SO}_{bm}$, $\text{R}(9)\text{R}(10)\text{N}-\text{CO}$, $\text{R}(11)-\text{CO}-$ or $\text{R}(12)\text{R}(13)\text{N}-\text{SO}_2-$,

where th perfluoroalkyl group is straight-chain

or branched,

X is oxygen, S or NR(14),
R(14) is H or (C₁-C₃)-alkyl,

bm is zero, 1 or 2,

5 p is zero, 1 or 2,

q is zero, 1, 2, 3, 4, 5 or 6,

R(8), R(9), R(11) and R(12) are, independently,
(C₁-C₈)-alkyl, (C₃-C₆)-alkenyl, -C_nH_{2n}-
R(15) or CF₃,

10 n is zero, 1, 2, 3 or 4,

R(15) is (C₃-C₇)-cycloalkyl, or phenyl
which is not substituted or is substituted
by 1-3 substituents from the group
F, Cl, CF₃, methyl, methoxy or NR(16)R(17)
with R(16) and R(17) being H or C₁-C₄-
alkyl,

15

where R(9), R(11) and R(12) also have the meaning
of H,

R(10) and R(13) are, independently,

20

H or (C₁-C₄)-alkyl,

where R(9) and R(10) and also R(12) and R(13) can
together be 4 or 5 methylene groups, of which one
CH₂ group can be replaced by oxygen, S, NH, N-CH₃,
or N-benzyl,

25

or

R(3) and R(4) are, independently of each other,

(C₁-C₈)-alkyl or -C_{a1}H_{2a1}R(18),

a1 is zero, 1 or 2,

R(18) is (C₃-C₈)-cycloalkyl, or phenyl

30

which is not substituted or is substituted
by 1-3 substituents from the group
F, Cl, CF₃, methyl, methoxy or
NR(19)R(20), with R(19) and R(20) being H
or CH₃,

35

or

R(3) and R(4) are, independently of each other,

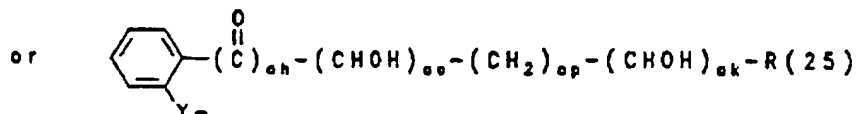
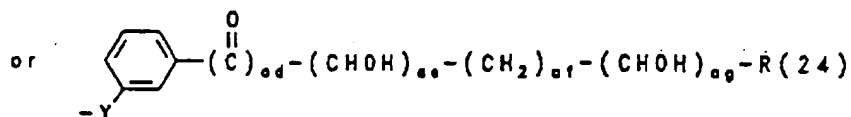
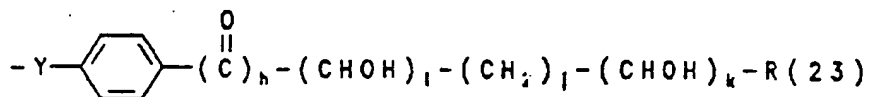
(C₁-C₉)-heteroaryl,

which is linked via C or N and which is unsubstituted
or is substituted by 1-3 substituents from

the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino or dimethylamino;

or

R(3) and R(4) are, independently of each other,



5 Y is oxygen, -S- or -NR(22)-,
 h, ad and ah are, independently, zero or 1,
 i, j, k, ae, af, ag, ao, ap and ak are,
 independently, zero, 1, 2, 3 or 4,
 where, however, in each case,

10 h, i and k are not simultaneously zero,
 ad, ae and ag are not simultaneously zero, and
 ah, ao and ak are not simultaneously zero,
 R(23), R(24), R(25) and R(22) are, independently,
 hydrogen or (C₁-C₃)-alkyl,

15 or

R(3) and R(4) are, independently of each other,
 hydrogen, F, Cl, Br, I, CN, (C₁-C₈)-alkyl, (C₁-C₈)-
 perfluoroalkyl, (C₃-C₈)-alkenyl or -C₅H₂₅R(26),

g is zero, 1, 2, 3 or 4,

20 R(26) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl
 or naphthyl,

where the aromatic radicals are not sub-
 stituted or are substituted by 1-3 sub-
 stituents from the group F, Cl, CF₃,
 25 methyl, methoxy or NR(27)R(28), with

R(27) and R(28) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

or

R(3) and R(4) are, independently of each other,

5 SR(29), -OR(30), -NR(31)R(32) or -CR(33)R(34)R(35);

R(29), R(30), R(31) and R(33) are, independently,

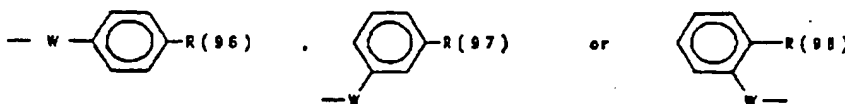
-C_aH_{2a}-(C₁-C₉)-heteroaryl

10 which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino or dimethylamino, a is zero, 1 or 2,

15 R(32), R(34) and R(35) are, independently of each other, defined as R(29), or are hydrogen, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

or

R(3) and R(4) are, independently of each other,



R(96), R(97) and R(98) are, independently, (C₁-C₉)-heteroaryl,

20 which is linked via C or N and which is unsubstituted or is substituted by 1-3 substituents from the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino, dimethylamino or benzyl,

25 W is oxygen, S or NR(36)-,

R(36) is H or (C₁-C₄)-alkyl,

or

R(3) and R(4) are, independently of each other,

R(37)-SO_{cm} or R(38)R(39)N-SO₂-,

30 cm is 1 or 2,

R(37) is (C₁-C₈)-alkyl, (C₁-C₈)-perfluoroalkyl,

(C₃-C₈)-alkenyl or -C₈H₂₈-R(40),

s is zero, 1, 2, 3 or 4,

R(40) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl.

or naphthyl,

where the aromatic radicals are not substituted or are substituted by 1-3 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(41)R(42), with R(41) and R(42) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

R(38) is H, (C₁-C₈)-alkyl, (C₁-C₈)-perfluoroalkyl, (C₃-C₈)-alkenyl or -C_wH_{2w}-R(43),

w is zero, 1, 2, 3 or 4,

R(43) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl or naphthyl where the aromatic radicals are not substituted or are substituted by 1-3 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(44)R(45), with R(44) and R(45) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl,

R(39) is H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl,

where R(38) and R(39) can together be 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

25 or

R(3) and R(4) are, independently of each other;

R(46)X(1)-,

X(1) is oxygen, S, NR(47), (D=O)A- or NR(48)C=MN^(*)R(49)-,

M is oxygen or S,

A is oxygen or NR(50),

D is C or SO,

R(46) is (C₁-C₈)-alkyl, (C₃-C₈)-alkenyl, (CH₂)_bC_dF_{2d+1} or -C_xH_{2x}-R(51),

b is zero or 1,

d is 1, 2, 3, 4, 5, 6 or 7,

x is zero, 1, 2, 3 or 4,

R(51) is (C₃-C₈)-cycloalkyl, phenyl, biphenyl, naphthyl,

where the aromatic radicals are not substituted or are substituted by 1-3 substituents from the group F, Cl, CF₃, methyl, methoxy, or NR(52)R(53); with R(52) and R(53) being H, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl;

5

R(47), R(48) and R(50) are, independently, hydrogen, (C₁-C₄)-alkyl or (C₁-C₄)-perfluoroalkyl,

10

R(49) is defined as R(46), where

R(46) and R(47) and, respectively, R(46) and R(48) can together be 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl,

15

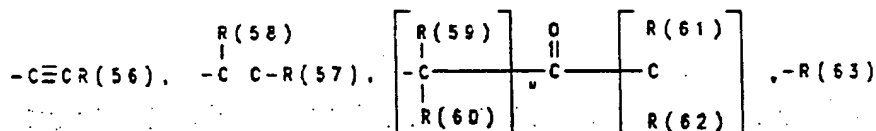
where A and N^(*) are bonded to the phenyl nucleus of the benzoylguanidine parent substance;

or

R(3) and R(4) are, independently of each other,

20

-SR(64), -OR(65), -NHR(66), -NR(67)R(68),
-CHR(69)R(70),



R(64), R(65), R(66), R(67) and R(69) are, identically or differently,

25

-(CH₂)_y-(CHOH)_z-(CH₂)_{aa}-(CH₂OH)_c-R(71) or
-(CH₂)_{ab}-O-(CH₂-CH₂O)_{ac}-R(72),

R(71) and R(72) are hydrogen or methyl,

u is 1, 2, 3 or 4,

v is zero, 1, 2, 3 or 4,

y, z and aa are, identically or differently,

30

zero, 1, 2, 3 or 4,

t is 1, 2, 3 or 4,
R(68), R(70), R(54) and R(55) are, identically or
differently,

hydrogen or (C₁-C₆)-alkyl, or
5 R(69) and R(70) and, respectively, R(54) and R(55)
are, together with the carbon atom carrying them, a
(C₃-C₈)-cycloalkyl;

R(63) is

10 H, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl or
-C_eH_{2e}-R(73),

e is zero, 1, 2, 3 or 4,

R(56), R(57) and R(73) are, independently,
phenyl,

15 which is unsubstituted or is substituted by 1-3
substituents from the group F, Cl, CF₃, methyl,
methoxy or NR(74)R(75) with R(74) and R(75)
being H or (C₁-C₄)-alkyl,

or R(56), R(57) and R(73) are, independently, (C₁-
C₉)-heteroaryl,

20 which is unsubstituted or is substituted as
phenyl;

R(58), R(59), R(60), R(61) and R(62) are hydrogen or
methyl,

or

25 R(3) and R(4) are, independently of each other, R(76)-NH-
SO₂-,

R(76) is R(77)R(78)N-(C=Y')-,

Y' is oxygen, S or N-R(79),

30 R(77) and R(78) are, identically or
differently,

H, (C₁-C₈)-alkyl, (C₃-C₆)-alkenyl,
or -C_fH_{2f}-R(80);

f is zero, 1, 2, 3 or 4,

35 R(80) is (C₅-C₇)-cycloalkyl, or
phenyl

which is unsubstituted or is sub-
stituted by 1-3 substituents from
the group F, Cl, CF₃, methoxy or
(C₁-C₄)-alkyl, or

R(77) and R(78) together form 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, S, NH, N- CH_3 or N-benzyl, where R(79) is defined as R(77) or is amidine;

5 or

R(3) and R(4) are, independently of each other, NR(84)R(85),

R(84) and R(85) are, independently of each other,

10

H or (C_1 - C_4)-alkyl, or, together, can be 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, S, NH, N- CH_3 or N-benzyl, or of which one or two CH_2 groups can be replaced by $\text{CH}-\text{C}_{dm}\text{H}_{2dm+1}$,

15

and the pharmaceutically tolerated salts thereof,

where, however, compounds are excepted in which the radicals R(1) to R(4) and also HA are combined in the following manner:

R(1)	R(2)	R(3)	R(4)	HA
CON=C(NH ₂)	H	H	Et	O
CON=C(NH ₂)	H	H	Me	O
CON=C(NH ₂)	H	H	H	O

20

2. A heteroarylguanidine I as claimed in claim 1, wherein:

25

HA is SO_m , O or NR(5),

m is zero, 1 or 2,

R(5) is hydrogen or methyl,

one of the two substituents R(1) and R(2) is

$-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$,

30

and whichever is the other is hydrogen, F, Cl, CH_3 , -OH or $-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$,

R(3) is hydrogen, F, Cl, Br, I, $-\text{C}\equiv\text{N}$, $\text{C}_q-\text{F}_{2q+1}$,

R(8)- SO_2 ,

R(9)R(10)N-CO, R(11)-CO- or R(12)R(13)N- SO_2 -,

where the perfluoroalkyl group is straight-chain or branched,

q is zero, 1, 2, 3, 4, 5 or 6,

R(8), R(9), R(11) and R(12) are, independently,

5 (C₁-C₈)-alkyl, (C₃-C₄)-alkenyl, -C_nH_{2n}-R(15) or CF₃,

n is zero, 1, 2, 3 or 4,

R(15) is (C₃-C₆)-cycloalkyl, or phenyl

10 which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(16)R(17), with R(16) and R(17) being H or methyl,

15 where R(9), R(11) and R(12) also have the meaning of H,

R(10) and R(13) are, independently, H or methyl,

or

20 R(3) is (C₁-C₈)-alkyl or -C_{a1}H_{2a1}R(18),

a₁ is zero, 1 or 2,

R(18) is (C₃-C₆)-cycloalkyl, or phenyl

25 which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(19)R(20), with R(19) and R(20) being H or CH₃;

or

30 R(3) is quinolyl, isoquinolyl, pyrrolyl, pyridyl or imadazolyl which are linked via C or N and which are unsubstituted or are substituted by 1 - 2 substituents from the group F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino or dimethylamino;

or

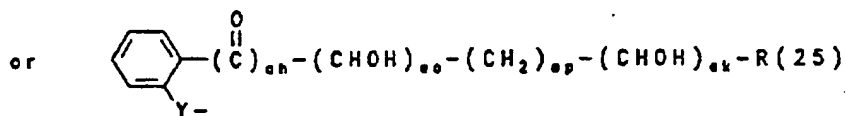
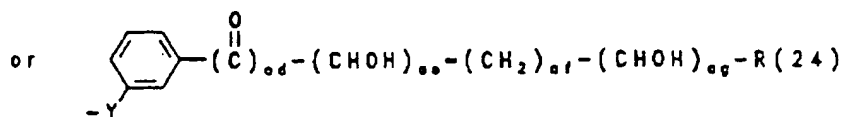
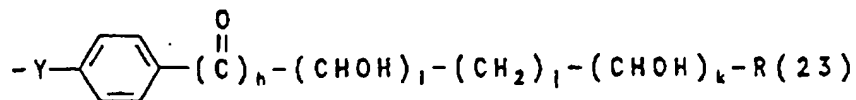
35 R(3) is -C=CR(56),

R(56) is phenyl,

which is unsubstituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(16)R(17), with R(16) and

R(17) being H or CH₃,

R(4) is



Y is oxygen, -S- or -NR(22)-,

h, ad and ah are, independently, zero or 1,

5 i, k, ag, ao and ak are, independently, zero, 1, 2 or 3,

j, af and ap are, independently, zero or 1,

where, however, in each case,

h, i and k are not simultaneously zero,

10 ad, ae and ag are not simultaneously zero, and

ah, ao and ak are not simultaneously zero,

R(23), R(24), R(25) and R(22) are, independently, hydrogen or methyl,

or

15 R(4) is hydrogen, F, Cl, Br, CN, (C₁-C₈)-alkyl, C_q-F_{2q+1}, (C₃-C₈)-alkenyl or -C_gH_{2g}R(25),

where the perfluoroalkyl group is straight-chain or branched,

q is zero, 1, 2, 3 or 4,

20 g is zero, 1 or 2,

R(26) is (C₃-C₈)-cycloalkyl, or phenyl

which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(27)R(28), with R(27) and

25 R(28) being H or CH₃,

or

R(4) is SR(29), -OR(30), -NR(31)R(32) or
-CR(33)R(34)R(35);

5 R(29), R(30), R(31) and R(33) are, independently,
-C_aH_{2a}-(C₁-C₉)-heteroaryl, selected from the group
consisting of pyrrolyl, imidazolyl, pyrazolyl and
pyridyl,

10 which is unsubstituted or is substituted
by 1 - 2 substituents from the group F,
Cl, CF₃, CH₃, methoxy, hydroxyl, amino,
methylamino or dimethylamino,

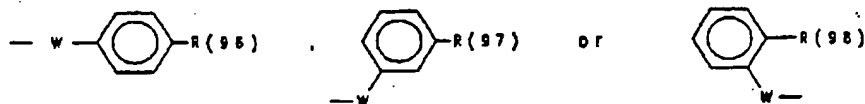
a is zero or 1,

R(32), R(34) and R(35) are, independently of each
other,

15 hydrogen or CH₃,

or

R(4) is



R(96), R(97) and R(98) are, independently, pyrrolyl,
imidazolyl, pyrazolyl or pyridyl,

20 which, in each case, is unsubstituted or is
substituted by 1 - 2 radicals from the group
comprising F, Cl, CF₃, CH₃, methoxy, dimethyl-
amino or benzyl,

W is oxygen, S or NR(36)-,

25 R(36) is H or methyl,

or

R(4) is R(37)-SO_{cm} or R(38)R(39)N-SO₂-,

R(37) is (C₁-C₆)-alkyl, CF₃, (C₃-C₄)-alkenyl or
C₆H_{2b}-R(40),

30 b is zero or 1,

R(40) is (C₃-C₆)-cycloalkyl, or phenyl

which is not substituted or is substi-
tuted by 1 - 2 substituents from the
group F, Cl, CF₃, methyl, methoxy or

NR(41)R(42), with R(41) and R(42) being H or CH₃,

R(38) is H, (C₁-C₄)-alkyl, CF₃, (C₃-C₄)-alkenyl or -C_wH_{2w}-R(43),

5 w is zero or 1

R(43) is (C₃-C₈)-cycloalkyl, or phenyl

which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(44)R(45), with R(44) and R(45) being H, (C₁-C₄)-alkyl or CH₃,

10

R(39) is H or CH₃,

where R(38) and R(39) can together be 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

15

or

R(4) is R(46)X(1)-,

X(1) is oxygen, S, NR(47), (C=O)A- or NR(48)C=MN^(*)R(49)-,

20

M is oxygen,

A is oxygen or NR(50),

R(46) is (C₁-C₆)-alkyl, (C₃-C₄)-alkenyl, (CH₂)_bC_dF_{2d+1} or -C_xH_{2x}-R(51),

25

b is zero or 1,

d is 1, 2, 3, 4, 5, 6 or 7,

x is zero or 1,

R(51) is (C₃-C₈)-cycloalkyl, or phenyl

which is not substituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(52)R(53); with R(52) and R(53) being H or CH₃,

30

R(47), R(48) and R(50)

are hydrogen or (C₁-C₄)-alkyl,

35

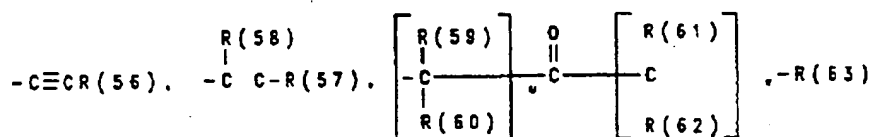
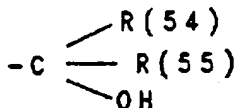
R(49) is defined as R(46), where

R(46) and R(47) and, respectively, R(46) and R(48) can together be 4 or 5 methylene groups, of which one CH₂ group can be replaced by

oxygen, S, NH, N-CH₃ or N-benzyl,
 where A and N(*) are bonded to the phenyl
 nucleus of the benzoylguanidine parent
 substance;

5 or

R(4) is -SR(64), -OR(65), -NHR(66), -NR(67)R(68),
 -CHR(69)R(70),



R(64), R(65), R(66), R(67) and R(69) are,
 identically or differently,

10 $-(CH_2)_y-(CHOH)_z-(CH_2)_{aa}-(CH_2OH)_t-R(71)$ or
 $-(CH_2)_{ab}-O-(CH_2-CH_2O)_{ac}-R(72),$

R(71) and R(72) are hydrogen or methyl,

u is 1 or 2,

v is zero, 1 or 2,

15 y, z and aa are, identically or differently,
 zero, 1 or 2,

t is 1, 2 or 3,

R(68), R(70), R(54) and R(55) are, identically or
 differently,

20 hydrogen or CH₃,

or

R(69) and R(70) and, respectively, R(54) and R(55)
 are, together with the carbon atom carrying them, a
 (C₃-C₆)-cycloalkyl;

25 R(63) is

H, (C₁-C₄)-alkyl, (C₃-C₆)-cycloalkyl or

-C_eH_{2e}-R(73),

e is zero, 1 or 2,

R(56), R(57) and R(73) are, independently,

30

phenyl

which is unsubstituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methyl, methoxy or NR(74)R(75), with R(74) and R(75) being H or CH₃,

5 or

R(56), R(57) and R(73) are, independently,

(C₁-C₉)-heteroaryl, selected from the group consisting of pyrrolyl, imidazolyl, pyrazolyl and pyridyl,

10

which is unsubstituted or is substituted as phenyl;

R(58), R(59), R(60), R(61) and R(62) are hydrogen or methyl,

or

15 R(4) is R(76)-NH-SO₂-,

R(76) is R(77)R(78)N-(C=Y')-,

Y' is oxygen, S or N-R(79),

R(77) and R(78) are, identically or differently,

20

H, (C₁-C₄)-alkyl, (C₃-C₄)-alkenyl or -C_fH_{2f}-R(80),
f is zero or 1,

R(80) is

(C₅-C₇)-cycloalkyl, or phenyl

25

which is unsubstituted or is substituted by 1 - 2 substituents from the group F, Cl, CF₃, methoxy or CH₃, or

30

R(77) and R(78) together form 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl, where

R(79) is defined as R(77),

or

35 R(4) is NR(84)R(85),

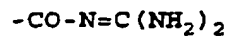
R(84) and R(85) are, independently of each other,

H or (C₁-C₄)-alkyl, or together form 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl,

or of which one or two CH_2 groups can be replaced by CH-CH_3 .

3. A heteroaroylguanidine I as claimed in claim 1, wherein:

5 R(1) is



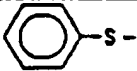



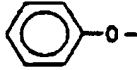



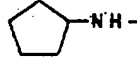
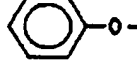
HA is

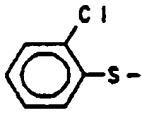

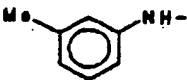
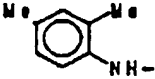

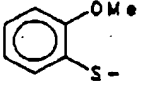
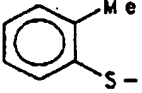
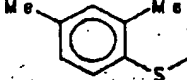

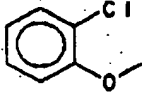
S, O, NH or NCH_3 ,


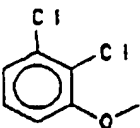

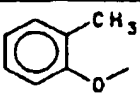

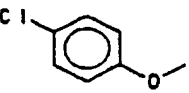

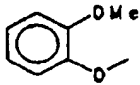
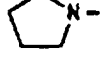
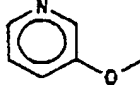
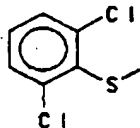
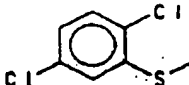

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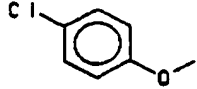
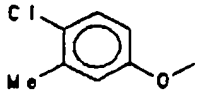
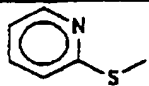
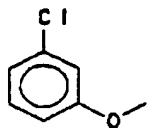

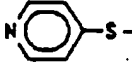


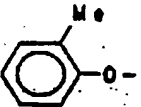
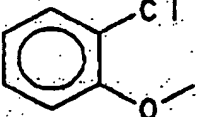
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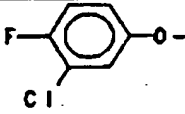


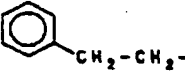
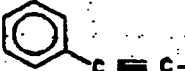
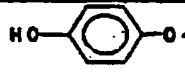

- 57 -

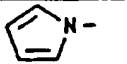

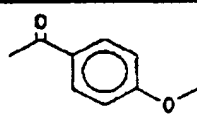
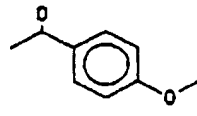
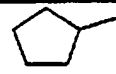
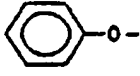
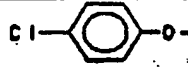



R(2)	R(3)	R(4)
H	n-BuNH-	Cl
H	H ₂ NSO ₂ -	
H	MeSO ₂	
H		Me
H		
H		Me
H		Cl
H		MeSO ₂ -
H	MeSO ₂	NH ₂
H	MeSO ₂ -	
H	MeSO ₂ -	



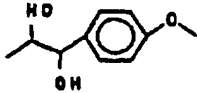

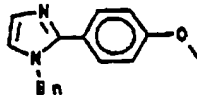
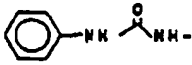
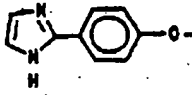
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	Cl-	
H	MeSO ₂ .	(CH ₃) ₂ -CHCH ₂ -O-
H	MeSO ₂ .	
H	MeSO ₂ .	
H	MeSO ₂ .	
H		

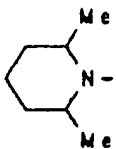
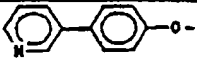
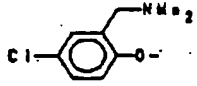

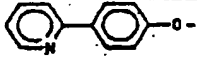
H		
H		
H		
H		
H		
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
Me	Me	H
H	MeSO ₂ ⁻	i-Pr
H	CF ₃	H
H		Cl
H	MeSO ₂ ⁻	MeNH-
H	MeSO ₂ ⁻	Et ₂ N-

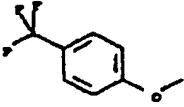
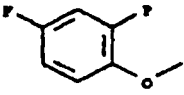
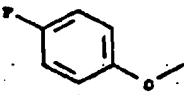
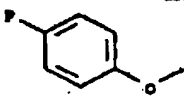
H	t-Bu	OH
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	2-Naphthyl
H	MeSO ₂ -	
H		Me
H		
H	Cl	Et ₂ N-
H	Me ₂ N-	H
H	MeSO ₂ -	

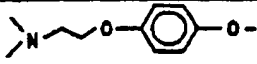
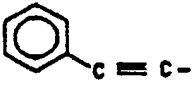

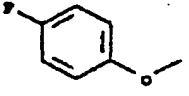
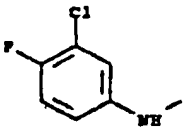
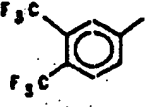
H	Br	NH ₂
H	Cl	H
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
H	CF ₃	CF ₃
H	Me	Me
H	I	CF ₃
H	Me	H
H	H	t-Bu
H	MeSO ₂ ⁻	
H	Me	Cl
H	Br	Me
H	Cl	MeO-
H	MeCO-	
H	Br	Br
H	MeSO ₂ ⁻	
H	MeSO ₂ ⁻	
NH ₂	Br	Me
H	Me ₂ N-	t-Bu
H	MeSO ₂ ⁻	
H		H

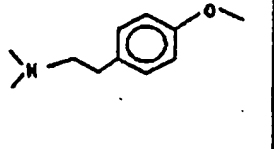
H		MeO-
H	Me	Br
H	Cl	F
H	t-Bu	H
NH ₂	Cl	H
H		Me ₂ N
H	Me ₂ N	Cl
H	MeSO ₂ -	7-Isoquinolinoxy
H	MeSO ₂ -	6-quinolinoxy
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeSO ₂ -	(CH ₃) ₂ CH-CH ₂ -
H	MeSO ₂ -	
H	Me ₂ N-	
H	Me ₂ N-	
H	Me	Me ₂ N-
H		
H	Me	
H	Cl	i-Pr

H		i-Pr
H	MeSO ₂ ⁻	5-quinolinoxy
H		CF ₃
H	i-Pr	MeSO ₂ ⁻
H	i-Pr	CF ₃
H	H	i-Pr
NH ₂	Br	Br
H	MeSO ₂ ⁻	
H		MeSO ₂ ⁻
H	MeSO ₂ ⁻	
H	Cl	
H	Me ₂ N	i-Pr
H	MeHN-	i-Pr
H	Cl	Cl
H	Cl	H ₂ N-
H	Cl	H ₂ N
H	MeSO ₂ ⁻	

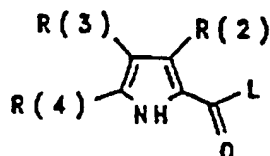
H	MeSO ₂ -	
H	Me ₂ N-	i-Pr
CF ₃	H	CF ₃
H	Br	Me
H	Me	Cl
H	Me ₂ N	Me
H	CF ₃	MeHN-
H	CH ₃ CO-	(CH ₃) ₂ CH-CH ₂
H	MeSO ₂ -	
H	CF ₃ -O-	H
H	Me	Me ₂ N
H	Cl	Me ₂ N-
H	MeSO ₂ -	
H	CH ₃ CO-	i-Pr
H	Br	BnO-
H	CF ₃	Br
H	i-Pr	MeO-
H	MeSO ₂ -	
H	MeSO ₂ -	
H	MeO-	t-Bu
H	Br	i-Pr
CF ₃	H	H
H	CF ₃	F

H	Ph	CF ₃
H	CF ₃	1-Imidazolyl
H	MeCO-	t-Butylmethyl
H	Br	F
H	Br	MeO-
H	CF ₃	PhO-
H	CF ₃	Cyclopentyl
H	MeSO ₂ -	Cyclobutyl
H	Me	CF ₃
H	MeSO ₂ -	
H	OH	t-Butyl
H	Cl	OMe
H	CF ₃	i-Pr
F	CF ₃	H
F	H	CF ₃
H	t-Butyl	OMe
H	MeCO-	
H	MeCO-	
H	t-Butyl	i-Butyl
H	CF ₃ CF ₂ -	i-Propyl
H	CF ₃ -SO ₂ -	
Cl	CF ₃	H

Cl	H	CF ₃
H	H	Perfluoro-i-propyl
H	H	H
H	MeSO ₂	
H	H	Perfluoro-n-propyl
H	CF ₃	
H	CF ₃	
H	CF ₃	
H	F	CF ₃
H	MeSO ₂	
H	t-Butyl	i-Propyl
H	t-Butyl	n-Butyl
H	i-Propyl	F
H	i-Butyl	F
H	Cl	1-Imidazolyl
H	H	CF ₃ -CF ₂
H	H	CF ₃
H	H	

H	MeSO ₂	
H	CF ₃ SO ₂	i-Propyl

4. A process for preparing a compound I as claimed in claim 1, wherein a compound of the formula II



- 5 in which L is a leaving group which can readily be substituted nucleophilically, is reacted with guanidine.
5. The use of a compound I as claimed in claim 1 for preparing a medicament for the treatment of arrhythmias.
6. A method for treating arrhythmias, wherein an effective quantity of a compound I as claimed in claim 1 is treated with the customary additives and administered in a suitable form for administration.
- 10 7. The use of a compound I as claimed in claim 1 for preparing a medicament for the treatment or prophylaxis of cardiac infarction.
- 15 8. The use of a compound I as claimed in claim 1 for preparing a medicament for the treatment or prophylaxis of angina pectoris.
9. The use of a compound I as claimed in claim 1 for preparing a medicament for the treatment or prophylaxis of ischemic conditions of the heart.
- 20 10. The use of a compound I as claimed in claim 1 for preparing a medicament for the treatment or prophylaxis of ischemic conditions of the peripheral and central nervous system and of stroke.
- 25 11. The use of a compound I as claimed in claim 1 for